

In the Claims:

123. (previously amended) A method of administering a glucagon-like peptide-1 (GLP-1) molecule by inhalation to the lungs of a patient for a time and under conditions effective to lower plasma glucose, wherein the GLP-1 molecule has an amino acid sequence of a formula:

$R_1$ -X-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Y-Gly-  
Gln-Ala-Ala-Lys-Z-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg- $R_2$   
(SEQ ID NO:1)

wherein:

$R_1$  is selected from the group consisting of L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, beta-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, and alpha-methyl-histidine;

X is selected from the group consisting of Gly, Val, Thr, Ile, and alpha-methyl-Ala;

Y is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

Z is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly; and

$R_2$  is selected from the group consisting of  $NH_2$ , and Gly-OH.

124. (previously added) The method of **Claim 123**, wherein the GLP-1 molecule is selected from the group consisting of Gly<sup>8</sup>-GLP-1(7-36) $NH_2$ , Val<sup>8</sup>-GLP-1(7-37)OH, alpha-methyl-Ala<sup>8</sup>-GLP-1(7-36) $NH_2$ , and Gly<sup>8</sup>-Gln<sup>21</sup>-GLP-1(7-37)OH.
125. (previously added) The method of **Claim 124**, wherein the GLP-1 molecule is

Val<sup>8</sup>-GLP-1(7-37)OH or Gly<sup>8</sup>-GLP-1(7-37)OH.

126. (previously added) The method of **Claim 125**, wherein the GLP-1 molecule is Val<sup>8</sup>-GLP-1(7-37)OH.
128. (previously added) The method of **Claim 123**, wherein the GLP-1 molecule is in the form of a dry powder.
129. (previously added) The method of **Claim 128**, wherein the dry powder has a particle size of about 10 microns mass median aerodynamic diameter.
130. (previously added) The method of **Claim 129**, wherein the dry powder has a particle size of less than 10 microns mass median aerodynamic diameter.
131. (previously added) The method of **Claim 130**, wherein the dry powder has a particle size of about 1 to about 5 microns mass median aerodynamic diameter.
132. (previously added) The method of **Claim 131**, wherein the dry powder has a particle size of about 2 to about 3 microns mass median aerodynamic diameter.
134. (previously added) The method of **Claim 128**, wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, a dry powder inhaler, and a sprayer.
135. (previously added) The method of **Claim 134**, wherein the device is a sprayer or a dry powder inhaler.
136. (previously added) The method of **Claim 135**, wherein an actuation of the device administers about 40 µg to about 4,000 µg of the GLP-1 molecule.
137. (previously added) The method of **Claim 136**, wherein an actuation of the

device administers about 80 µg to about 2,000 µg of the GLP-1 molecule.

138. (previously added) The method of **Claim 137**, wherein an actuation of the device administers about 160 µg to about 1,000 µg of the GLP-1 molecule.
139. (previously added) The method of **Claim 138**, wherein an actuation of the device administers about 320 µg to about 500 µg of the GLP-1 molecule.
140. (previously added) The method of **Claim 123**, wherein the GLP-1 molecule is administered as an aerosol.
142. (previously added) The method of **Claim 140**, wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, and a sprayer.
184. (currently amended) A method of administering a GLP-1 molecule by inhalation to the lungs of a patient for a time and under conditions effective to lower plasma glucose, wherein the GLP-1 molecule comprises an amino acid sequence of a formula:

R<sub>1</sub>-X-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Y-Gly-  
Gln-Ala-Ala-Lys-Z-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-R<sub>2</sub>  
(SEQ ID NO:1)

wherein:

R<sub>1</sub> is selected from the group consisting of L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, beta-hydroxy-histidine, homohistidine, alpha-fluoromethyl-histidine, and alpha-methyl-histidine;

X is selected from the group consisting of Gly, Val, Thr, Ile, and alpha-methyl-Ala;

Y is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly;

Z is selected from the group consisting of Glu, Gln, Ala, Thr, Ser, and Gly; and

R<sub>2</sub> is selected from the group consisting of NH<sub>2</sub>, and Gly-OH

~~GLP-1 analog with alanine at position 8 substituted with an amino acid selected from the group consisting of valine, glycine, or alpha-methyl alanine~~  
and wherein the GLP-1 molecule further comprises one additional substitution compared with GLP-1.

185. (currently added) The method of **Claim 184** wherein ~~alanine at position 8~~ X is ~~substituted with~~ valine.
186. (currently added) The method of **Claim 184** wherein ~~alanine at position 8~~ X is ~~substituted with~~ glycine.
187. (previously added) The method of **Claim 185** wherein the GLP-1 molecule is in the form of a dry powder.
188. (previously added) The method of **Claim 187** wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, a dry powder inhaler, and a sprayer.
189. (previously added) The method of **Claim 185**, wherein the GLP-1 molecule is administered as an aerosol.
190. (previously added) The method of **Claim 189**, wherein the GLP-1 molecule is delivered from an inhalation device is selected from the group consisting of a nebulizer, a metered-dose inhaler, and a sprayer.

191. (previously added) The method of **Claim 186** wherein the GLP-1 molecule is in the form of a dry powder.
192. (previously added) The method of **Claim 191** wherein the GLP-1 molecule is delivered from an inhalation device selected from the group consisting of a nebulizer, a metered-dose inhaler, a dry powder inhaler, and a sprayer.
193. (previously added) The method of **Claim 186**, wherein the GLP-1 molecule is administered as an aerosol.
194. (previously added) The method of **Claim 193**, wherein the GLP-1 molecule is delivered from an inhalation device is selected from the group consisting of a nebulizer, a metered-dose inhaler, and a sprayer.

#### **Remarks**

In this response, Applicants have amended claims 184, 185, and 186. Support for the amendments to these claims can be found throughout the specification and in particular on page 9, lines 1 to 15 and page 7, lines 28 to 30. Applicants were the first to demonstrate that GLP-1 molecules can actually be administered by inhalation to the lung, absorbed into the blood and lower plasma glucose levels. Applicants have amended the claims to a well-defined genus of GLP-1 molecules with a defined structure as presented in a formula. Applicants respectfully request that the claims be allowed given the technical contribution to the art.

#### **REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAPH**

Claims 184-194 stand rejected under 35 U.S.C. § 112(2) as being indefinite. Specifically, the Examiner asserts that it is unclear as to what "position 8" refers to in the claims. To put the claims in allowable format, Applicants have amended the claims to remove the reference to "position 8." The Examiner's rejection is now rendered moot. Thus, Applicants respectfully submit that the §112(2) rejection should be withdrawn.